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The Aetiology of Congenital Abnormalities

By J. EDGAR MORISON,

Department of Pathology, Queen's University, Belfast.

GROSS abnormalities are fortunately not common. Murphy (1940) in Philadelphia found that approximately 47 individuals possessing congenital malformations were born alive or dead per 10,000 live births. About one-quarter of these were reported as stillbirths. His data was collected mainly from death certificates and included only the grosser defects. Malpas (1937) recorded 294 cases in 13,964 consecutive births in Liverpool.

The occurrence of any congenital abnormality is especially painful to all concerned, and the parents will wish to know the cause of the condition, and whether it is likely to recur in subsequent pregnancies. It is not possible to give a satisfactory answer to these questions, but it may be useful to survey some recent contributions to the problem, to indicate in what directions progress may be expected, and to acknowledge the valuable contributions made in allied fields of biological science.

As an individual, developed from the fusion of the sex cells or gametes of his parents, grows through intra-uterine and extra-uterine life his whole being expresses the result of the interaction of his genetic pattern or constitution with the environment. The environment is at first the seemingly constant one of the uterus, and here the internal environment is determined primarily by such substances as can pass across the placenta. The genetic pattern is a mosaic inherited from his parents and more remote ancestors. It is composed of unit characteristics, or traits, all of which the geneticist hopes some day to recognise individually, and to trace as they are transmitted as physical entities, or genes, from generation to generation on the chromosomes of the sex cells. In accordance with the modern knowledge of Mendelian inheritance some of these characters or traits may not have been expressed for generations; either because they are recessive and have not been present as homozygotes, or because other genes or environmental factors have modified their expression. The present enquiry is concerned with the relative importance of genetic influences and the intra-uterine environment on the development of such variations from the normal as can be usefully recognised. These

variations are usually malformations or abnormalities of bodily form, but an increasing number of disturbances of physiological function will be recognised as biochemical and biophysical studies are pursued.

It is well known that in certain families abnormalities recur generation after generation in such a manner that the genetic mode of their inheritance can be demonstrated. One of the most striking examples is given by Drinkwater (1917). The skeleton and the effigy of the first Earl of Shrewsbury, a hero of the French wars of the fifteenth century, showed a fusion of the proximal and middle phalanges of certain digits. A lineal descendant fourteen generations later showed the same rare condition and knew of its existence in his father and grandfather. In the Nougaret pedigree dating from about 1637 there were 134 individuals affected with a form of night blindness (Roberts, 1940). Such abnormalities fail to interfere with reproduction and are among the more fundamental and elementary observations of medical genetics. The present problem is the occurrence of an individual, who is often so grossly malformed as to be described as a monster, in a family where there may be no previous history of any such disaster. Throughout his history mankind has questioned the meaning and significance of such visitations, and it may be of interest to describe some of the older beliefs. The relevant literature is fully listed by Ballantyne (1904).

Historical Review.

Three distinct trends of thought may be recognised, they were never necessarily exclusive of each other, but in different periods and countries varying emphasis was laid upon each of them, and they found expression in a diversity of terms.

The oldest, and at all times the most widespread, belief was in the Supernatural origin of monsters. Some have maintained that ancient peoples fashioned their gods in the shape of these human and animal monsters. Perhaps among the Greeks the Centaur was an infant born with two pairs of lower limbs or a hydrocephalic calf, Atlas a case of occipital encephalocele and the Gorgon's head an acormic placental parasite. The god Pthah of the Egyptians certainly appears to represent an achondroplasic dwarf. Some peoples believed that the gods amused themselves by creating such forms, others, however, looked upon such occurrences as portents of the future which were sent to warn or admonish them. A tablet from ancient Nineveh reveals that the birth of a baby with an imperforate anus meant famine, but that a child seeming to possess three legs indicated great prosperity. Many infants, and indeed many mothers, were sacrificed to such beliefs. In the early Christian era there was an increasing pre-occupation with the idea of sin, and the birth of such offspring was regarded as punishment for the sins of the parents. Sometimes the abnormality was thought to proclaim the greater glory of God. As the antithesis between good and evil, between the all good God and the evil one, became clearer malformations appeared rather to be the work of the Devil.

But while the ignorant mass subscribed to such doctrines there were those who looked for natural physical causes. Aristotle and the Greeks speculated on this

and their speculations were handed on through the Arab physicians of the pre-Renaissance period. Though based on no accurate knowledge of reproduction these doctrines influenced the physicians and philosophers of the sixteenth and seventeenth centuries. About this time there was a greater diversity of opinion as to the fundamental cause of these conditions than at any time in the world's history. Supernatural theories, theories of hybridity and the bestial origin of defects struggled with theories ascribing them to emotional strains and stresses.

The belief in the importance of mental or emotional causes is very ancient. According to the writer of the Genesis narrative (Gen. xxx) Jacob made use of it in stock rearing. Roman, Jewish and early Christian writers acknowledged the importance of mental impressions, especially at the time of conception. That emotional trauma to the mother at any time during pregnancy could serve as the cause of gross malformations was probably a contribution of the Revival of Learning in Europe and a revulsion from the crude beliefs in the Powers of Evil. The emotional incident was not necessarily specific, but hairy children occasioned by the sight of monkeys, and anencephalic infants produced by handling frogs, were attractive forms of this speculation. A few shrewd criticisms were made such as that few children should be born without defects. Doubt was also expressed as to whether these influences could operate after the child was fully formed about the seventh week after conception. The belief, however, gained wide acceptance and, even in the later half of the nineteenth century, it persisted in American medical literature.

It is apparent that no satisfactory explanations have been provided in the past. A belief in the importance of maternal emotional strain or shock persists even to-day among the laity. There is not one shred of evidence in its favour. Modern embryology has shown that the disturbances of normal growth responsible for the abnormalities described must occur in the early stages of embryonic development, and usually long before the eighth week of intra-uterine life. Perhaps this is an even more convincing argument than the absence of any nerve pathway between the mother and the fœtus, because the alleged psychic traumatisation usually occurred late in pregnancy and therefore could not have been significant. The enormous teratological literature of the seventeenth to nineteenth century is nothing but futile speculations over mere coincidences. Similar chronological considerations dispose of all but a fraction of cases where physical trauma to the pregnant woman has been alleged to produce fœtal abnormalities.

The Pre-Natal Environment.

The relative contribution to the development of the ovum made by the genetic constitution and by subtle, and as yet unknown, changes in the intra-uterine environment and nutrition remains a major problem in biology. Experimental embryologists, concerned with free living embryos of lower forms of life, have described the production of many monstrous forms by refrigeration and by the addition of magnesium chloride, alcohol and other substances to the medium (Stockard, 1921). Modern embryology conceives of the embryo as the site of

many loci of cells growing and differentiating at different rates at different periods in their development. This activity is directed by chemical substances called "organisers," and it is determined primarily by the genetic constitution of the individual. Especially in the lower forms of life an enormous mass of information has accumulated on the morphogenetic interrelationship of embryonic parts, but no coherent picture of the whole has emerged. It is not difficult to believe that an adverse environment will act selectively, probably on areas at the moment the site of most active growth, or that certain substances in very low concentration might interfere specifically with the activity of the organisers, either directly or by co-enzyme inactivation or substrate blockage. An inadequacy or omission of any stage in embryonic development cannot be repaired at a later stage. If determined by environmental changes these need only act for a short time. Experimental work on lowly forms of life can only be transferred to mammals, and especially to man, with very great caution. The mechanism of intra-uterine nutrition has been subjected to prolonged evolution and is well adapted to the preservation of a constant environment. For the embryo or fœtus this stability is of the highest survival value and it may be assumed that the mechanism has become highly efficient. That highly specific effects could be explained as due to changes in environment will not prove that human abnormalities are produced in this way. The production of abnormalities, even in mammals, and still less their production in lower forms, by highly artificial agents will not necessarily bear any relationship to their actual mode of production. Experimental embryology, like experimental carcinogenesis, is in some danger of mistaking the mere accumulation of facts for knowledge.

Mall (1908) produced evidence suggestive of the importance of the environment as modified by abnormalities of placental implantation. He found that 96 per cent. of the embryos in unruptured tubal gestations and 7 per cent. of those aborted from the uterus were abnormal. He considered that the argument against the germinal origin of pathological ova and monsters was overwhelming. While lethal genetic factors might determine abortion from the uterus it is more difficult to see how any genetic factor carried by the ovum could influence its implantation in the tube. This suggests that improper nutrition can produce abnormal embryos; it does not prove that monsters, associated with gestations which are better implanted and which proceed to term or near it, are produced in this way. Greenhill (1939) found an incidence of 2.5 per cent. of monsters in 4,446 cases of placenta prævia as compared with 0.94 per cent. for all obstetric cases. Before attaching importance to this as evidence of environmental influences it would be necessary to show that the low implantation interfered with transplacental nutrition early in pregnancy, and also that placenta prævia itself was not an associated genetic defect.

That specific insufficiencies in embryonic nutrition may sometimes determine congenital defects is strongly suggested by the work of Warkany (Warkany, Nelson and Schraffenberger, 1942, 1943; Warkany and Schraffenberger, 1944). Cleft palate and various bony deformities of the limbs were produced. These results

were obtained with a riboflavin deficient diet and in the Sprague-Dawley and Baltimore strains of rats, and by Noback and Kupperman (1944) in the Wistar strain. Genetic influences would, therefore, appear to play little part in these experiments. At most dietary surveys (Murphy, 1939, Burke and others, 1943) suggest a slightly higher incidence of dietary insufficiency among the mothers of malformed infants. The maternal reserves of most dietary constituents are unlikely to be as greatly strained during the early formative and critical period of embryonic development as later when the fœtal demands grow. Only occasionally have dietary deficiencies been recognised as the cause of disease in late fœtal life. Maxwell, Hu and Turnbull (1932) described fœtal rickets in the offspring of mothers with active osteomalacia. A search for other specific defects arising in late fœtal life should produce some results of interest, if maternal dietary deficiencies are of significance at any period.

In the past embryonic and fœtal inflammation, usually ascribed to intra-uterine infection, was thought to be frequent, and to be of great importance in the production of congenital abnormalities. It was thought to be of special importance in the amniotic sac, in the meninges and brain and in the heart. The histological evidence offered cannot be accepted. Streeter (1930) attacked the popular idea that amniotic inflammation, adhesions and mechanical constriction dictated intra-uterine amputations. He believed that the defects were due to imperfect development of limb-buds, comparable to doubling, hypertrophy and other defects of digits and limbs, and that the formation of adhesions and annular bands was secondary to nutritional changes. Very similar defects of limbs have been shown to be primary and due to hereditary factors.

Recent observations from Australia, described by Gregg (1941), Swan (1944) and Evans (1944), have shown what appears to be a significant association between maternal rubella in the first few months of pregnancy and the development of various congenital defects. These lesions include a hitherto undescribed form of congenital cataract (Gregg), deaf-mutism, heart disease, microcephaly and major dental anomalies (Evans, 1944). Reese (1944) and Erickson (1944) have already reported similar cases from America. Studies such as this depend on the collaboration of many outside the research itself, and are very liable to suffer from a failure to report negative cases. The association of the defect with illness in the early months of pregnancy is, however, very suggestive. It is possible that an aberrant form of German measles is responsible, but the probable penetration of the placental barrier by a virus disease in the early months of pregnancy is of very great interest. The only disease known to be spread from mother to child in utero with any frequency is syphilis, and here it is doubtful if infection of the fœtus can occur before the fourth month. The fœtus may be grossly affected, development may be retarded and it may die, but the incidence of malformations is not affected.

The author is not aware of any adequate scientific study of the effect of contraceptive techniques on the incidence of abnormalities. Several studies by partisans have appeared, but beliefs are no substitute for the accumulation and analysis of facts.

The marked increase in the incidence of defects, such as anencephaly (Malpas, 1937) and Mongolism (Penrose, 1932), with increase in maternal age is not evidence that the maternal environment produces the lesion. It suggests that it facilitates in varying degree the expression of a defect already present, and a possible genetic basis for Mongolism has been discussed by Penrose (1932). Studies on the incidence of abnormalities in different groups of the population must take such contributory factors into account.

Genetic Influences.

The science of modern genetics has progressed far beyond the study of simple dominant and recessive inheritance and the study of family trees. Statistical analysis has overcome some of the difficulties imposed by our inability to conduct selective breeding in man. Genetic considerations have been applied to conditions where the frequency of expression of a trait is low, compared to the frequency with which it is inherited, and to conditions which depend on interaction between inherited factors and the environment—for example, tuberculosis (Kallmann and Reisner, 1943).

It must be admitted that little real progress has yet been made with the analysis of the more common congenital abnormalities in man, such as anencephaly, spina bifida, some skeletal defects and Mongolism. Certain defects of the limbs, such as some forms of syndactyly, brachydactyly and polydactyly, some forms of hare-lip and cleft palate, and certain rare skin and nervous diseases are recognised as being determined, at least principally, by genetic factors. On the other hand Gruneberg (1943, 1944) has been able to study a wide range of comparable abnormalities in laboratory rodents, chiefly mice, and by selective breeding he has shown beyond doubt that many are genetic and often determined by simple recessive genes.

For the relative failure of genetic methods in the study of congenital abnormalities of man a number of causes must be considered. Some of these are common to any study of human genetics, such as the uncertainty as to whether the results produced by homozygous and heterozygous dominant genes are necessarily comparable. There is also uncertainty as to the relationship of certain abnormalities to one another. Not infrequently abnormalities are multiple and embryology does not yet enable us to refer them to a single developmental error, or to decide if they are necessarily related. Conditions such as anencephaly and various forms of spina bifida may be due to variations in the expression of a common defect. Again certain apparently similar end results may not be produced in the same way and may thus be fundamentally different. Surveys are also greatly hampered by the early death of many affected individuals, and by the extremely vague information which is usually available at the time of enquiry. A very serious source of difficulty is the probable loss of many of the affected individuals without any possible record by abortion and early miscarriage. The observations of Mall (1917) would suggest that many monsters fail to develop. He found that for each case appearing at term twelve others died and were aborted. Schultze (1940) believed that about one abortion occurred for every six live births, and that one abortion due to germ plasm defect might be expected for every thirteen live births. These monsters may not

all be identical ætiologically with those which survive to later in pregnancy, but the subject has been little studied and the position is very unsatisfactory. This problem of early intra-uterine death is a very pressing one and some geneticists (Penrose, 1932) have made assumptions which are in urgent need of proof, if they are to be applied to this field.

The construction of family trees is obviously useless in these cases. It might be thought that the brothers and sisters of the affected individuals would provide some information. These siblings are undoubtedly much more likely to be affected than non-related children. Macklin (1936) reviewed 1,420 cases from the literature and 311 of these were in families where more than one child was affected. In these affected siblings the defect was identical in 80 per cent. of cases. Murphy (1940) found the rate in families already having one defective child was approximately twenty-four times greater than in the general population, and that in about half of these cases the defects were identical in the siblings. Malpas found only twelve recurrences in 863 fraternities where one child was affected. He pointed out that recurrence only indicated that the maternal factors which determined malformations persisted, or recurred, in successive pregnancies, although it certainly showed that they were profound and permanent and far removed from the category of casual influences. On this view cyclic fluctuations in the conditions responsible in the maternal environment must occur, because normal children are often born between children with identical defects. It may well be urged that this requires an impossibly complex conception of these maternal or environmental factors.

There are a few observations on the occurrence of abnormalities and their duplication in near relatives (Murphy, 1940). The incidence recorded was three times as high on the maternal as on the paternal side, and this is not consistent with modern theories of inheritance. However, the information was obtained by home visiting and a questionnaire and was very probably incomplete. Important evidence pointing to inheritance of recessive traits is often afforded by an excess of cousin marriages among the parents. About 0.6 to 0.8 marriages are between cousins. However, unless a trait is much rarer than 1 in 3,000, a very large number of cases will have to be studied before any evidence can be provided in this way. When a trait is inherited by dominant or intermediate transmission, but only sometimes expressed, the frequency of expression remains constant when different generations are compared. It is evident that much larger samples must be accurately collected and correlated before either of these methods can be expected to yield results in the study of the inheritance of congenital defects.

A paramount difficulty when abnormal offspring are produced by normal parents, and do not themselves reproduce, is the impossibility of establishing a correlation between the defects of one generation and the next. It is here that the modern techniques of linkage study, especially those which may be applied to a single generation, such as the method described by Penrose (1935), will prove of value. It is necessary, however, first to determine a large number of readily detectable and particulate hereditary characters, preferably, at least one represented by a gene carried on each chromosome. It is here that the modern work on the genetics

of the blood groups is of the very greatest importance. Work on the identification and correlation of a multitude of normal hereditary characteristics is the first necessity. Afterwards, the study of a very large number of families with affected siblings will be necessary. If any progress is to be made in this subject it is becoming apparent that the study of defective individuals will have to be made, not by an individual, or even in one medical centre, but on a nation wide scale.

Genetic Mutations.

Haldane (1935) showed that in order to maintain the proportion of hæmophiliacs approximately constant it was necessary that fresh genes capable of producing the condition should spontaneously appear to replace those lost by the failure of many of the sufferers to produce offspring. If this did not occur the present incidence would require that the whole male population of England suffered from hæmophilia at the time of the Norman Conquest. He calculated that one mutation in 50,000 X-chromosomes was required to balance the elimination of the hæmophiliac gene. The rare disease epiloia is inherited as an autosomal dominant, yet cases occur with normal parents. Gunther and Penrose (1935) produced evidence that a gene mutation is responsible for this, and that it occurs in between one in 60,000 and one in 120,000 of the population. The occurrence of such apparently spontaneous mutations in the chromosomal structure of normal germ cells might seem to provide an explanation for the occurrence of congenital abnormalities. There is considerable evidence from lower animals that these figures for mutation rates are relatively high. It would seem that mutations could, at most, explain only a rather small percentage of abnormalities. Similar, but usually favourable, mutations are the basis of organic evolution, and the modern Mendelian system of evolution, unlike the Darwinian, does not require a high mutation rate. It is possible that some abnormalities appear as the result of gene mutations, and the loss of affected offspring without issue would require some such process, if the incidence of an abnormality is to remain constant. If abnormalities are determined by genetic factors any real change in their incidence carries with it important biological implications concerning the raw material of organic evolution.

The mutation rate can be greatly increased in an entirely non-selective manner by exposure to X-rays, radium, free electrons and neutrons. In mammals Bagg (1929) produced various deformities in mice by exposing the parents to X-rays. These malformations were transmitted to offspring for generations. It is, however, doubtful if defects are ever produced in this, or any comparable manner, in human beings.

Conclusions.

There seems little hope that the problem of the ætiology of congenital abnormalities will be solved within the near future. There is little evidence that changes in the maternal or intra-uterine environment, consistent with the maintenance of pregnancy, can have any specific effect. The evidence in favour of the importance of the environment is probably strongest when abnormalities, which may be explained as the result of incomplete twinning, are considered. There is satisfactory

evidence that many congenital abnormalities are due to the inheritance of hereditary taints carried on genes. Many other defects are probably also genetic in origin, but the evidence remains insufficient. The expression of these defects is perhaps modified sometimes by the intra-uterine environment, but it must be appreciated that very variable effects may be produced by an identical gene against the infinitely variable background of the different assortments of genes present in different individuals. Until large accumulations of data, accurately recorded at the time, and based upon very extensive analysis of the transmission of associated hereditary traits, are available little progress need be expected. Progress may also be delayed by lack of information concerning abortions and early miscarriages.

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